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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/784,674	02/15/2001	Karen W. Shannon	10971464-3	3167

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AGILENT TECHNOLOGIES, INC.
INTELLECTUAL PROPERTY ADMINISTRATION, LEGAL DEPT.
P.O. BOX 7599
M/S DL429
LOVELAND, CO 80537-0599

EXAMINER	
MAHATAN, CHANNING	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/784,674	SHANNON ET AL.	
	Examiner	Art Unit	
	Channing S. Mahatan	1631	

-- Th MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40 and 98-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40 and 98-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

APPLICANTS' ARGUMENTS

Applicants' arguments filed 03 October 2003 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

New art rejections have been applied upon further consideration of U.S. Patent Number 6,251,588 (U.S. Application Number 09/021,071).

CLAIMS UNDER EXAMINATION

Claims herein under examination are claims 1-40 and 98-101. Claims 41-97 have been cancelled as indicated in Paper No. 13, filed 24 February 2003.

TERMINAL DISCLAIMER

The 'Terminal Disclaimer' filed 03 October 2003 has been approved.

Claims Rejected Under 35 U.S.C. § 112 1st Paragrah

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 U.S.P.Q. 546 (B.P.A.I. 1986) and reiterated by the Court of Appeals in In re Wands, 8 U.S.P.Q. 2d 1400 at 1404 (C.A.F.C. 1988). The factors to be considered in determining whether undue experimentation is required

include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

SCOPE OF ENABLEMENT

Claims 25-27 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a dimensionless equation (pages 37-38 of the Specification), does not provide enablement for all/other types of equations to convert parameters into dimensionless numbers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope. Absent from the specification is guidance regarding the utilization of alternative equations. The specification teaches only one method/equation for the conversion of parameters into dimensionless values (pages 37-38), and the claims are not so limited. Therefore, the instant claims embrace more than what is taught in the original disclosure. Again no other methods of deriving a dimensionless value are disclosed. No guidance, direction, or examples are provided such that one of ordinary skill in the art would have known practice how to make and use the claimed invention commensurate in scope with the claims.

Claims Rejected Under 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1-3, 5-10, 15, 17-22, 98, and 100 under 35 U.S.C. § 102(b) as being anticipated by Hyndman et al. (Software to Determine Optimal Oligonucleotide Sequences Based on Hybridization Simulation Data. Biotechniques. 1996, Volume 20, Number 6, pages 1090-1096) as indicated in the office action, mailed 01 July 2003, are maintained for reasons of record.

Hyndman et al. describes a computer program which simulates actual hybridization experiments between probes (RNA and DNA) and sequences (RNA and DNA) in a database through the creation of a set of candidate oligonucleotides from a target gene, wherein each candidate oligonucleotide is searched for in a large sequence database for sequences that will hybridize to the oligonucleotide (Abstract; page 1091, column 1, lines 28-31; and Figure 2). A probe set is created (capable of being edited; i.e. the complement or a tag sequence (chemically modified nucleotide) can be added), containing all possible oligonucleotides derived from the target sequence which fits a chosen specification, such as specified length (interpreted to include probes of identical length), melting temperature, or free energy of hybridization (page 1091, column 2, lines 13-28). The computer hybridization simulation determines the specificity of each sequence to which a particular probe may hybridize (i.e. binding strength) then selects the most favorable/stable probes (pages 1091-1092, columns 2-1, lines 29-37 and 11-10,

respectively). The authors describe the application of HYBsimulator™ to identify common/census probes (i.e. clustered along a region) to all the targets of interest (same gene in related organism or related genes in the same organism or unknown varieties of a gene family) (page 1094, column 1, lines 20-39 Common or Consensus Probes section). Therefore, Hyndman et al. identifies a probe set (i.e. non-identical oligonucleotides within a nucleotide sequence) hybridizable to a target sequence; the probes within the probe set are evaluated for a hybridizing parameter; a subset of most favorable/stable probes are selected from the evaluated probe set; common/consensus probes are designed to all target sequences resulting in the identified and selected of probes clustered along a region (common/consensus). Thus, Hyndman et al. anticipates the claimed invention.

Applicants' argues in the response filed 03 October 2003 that Hyndman et al. "does not disclose the step of identifying oligonucleotides in a subset of oligonucleotides that are clustered along a region of the nucleotide sequence that is hybridizable to the target nucleotide sequence" and that the present "methods are based upon Applicants' discovery that oligonucleotides showing high hybridization efficiencies tend to form clusters", and that the present "seeks to select good probes without performing full thermodynamic and other studies". These arguments are found unpersuasive as clarified by the Examiner (above). Additionally, Applicants' claimed invention is not reflective of the limitation for selecting oligonucleotides showing high hybridization efficiencies to form clusters as argued or the selection of "good" probes.

Claims 1-10, 15-17, 21, 23, 28, 37, 39, 40, 98, and 100 are rejected under 35 U.S.C. § 102(b) as being anticipated by Rychlik et al. (A computer program for choosing optimal

oligonucleotides for filter hybridization, sequencing and in vitro amplification of DNA. Nucleic Acids Research. 1989. Volume 17, pages 8543-8551).

Rychlik et al. presents a method/computer program for the selection of optimal oligonucleotides for filter hybridization, primers for sequencing, or primers for DNA amplification wherein the stability of the duplex formed between the probe and target nucleic acid, specificity of the probe for the intended target sequence, and self-complementarity are considered to determine probe quality (Abstract). The computer program computes DNA duplex stability (T_d) values based on nearest neighbor thermodynamic parameters (Abstract; page 8544, lines 8-10; and page 8545, lines 2-15). The determination of self complementarity is defined as where the 5' terminal sequence of given oligonucleotide is aligned with the adjacent sequences (Figure 1A). After determination of base pairing, the 5'-terminus is repositioned one nucleotide closer to the 3'-terminus and the oligonucleotides are checked for base pairing again. The authors evaluate palindromic oligonucleotide segments (page 8545-8547, beginning on line 31), wherein self-complementary palindromes are described and depicted (Figure 1) as being side by side positioning of complementary segments which may form said palindrome (i.e. clusters of oligonucleotide sequences). It is noted that the instant claims are not limited as to the size, number, or complexity of the cluster identification. Thus, Rychlik et al. anticipates the claimed invention.

Claims 1-10, 15, 16, 18, 20, 21, 23, 28, 37, 39, 40, 98, and 100 are rejected under 35 U.S.C. § 102(b) as being anticipated by Mitsuhashi (U.S. Patent Number 5,556,749).

Mitsuhashi et al. (U.S. Patent Number 5,556,749) discloses an oligoprobe designstation allowing a user to calculate and design specific oligonucleotide probes for DNA and mRNA

hybridization procedures (Abstract). Candidate probes are analyzed for their binding specificity relative to some known set of mRNA or DNA sequences (i.e. sequence database) (Column 6, lines 31-34). Mitsuhashi et al. describe the process of probe design as follows: 1) candidate probes are selected at some or all the positions along a given target; 2) a melting temperature model is selected, and an accounting is made of how many false hybridizations each candidate probe will produce and what the melting temperature will be; 3) results are presented with a unique set of tools for visualization, analysis, and selection among the candidate probes (i.e. clustering) (Column 6, lines 34-50 and Columns 11-26). The designstation graphically displays of the results thereby providing the user with the ability to visualize hybridization strengths (i.e. T_m) and false hybridizations (various sources and temperatures) for all candidate oligonucleotide probes for the target sequence (Column 10, lines 41-59 and Figure 4).

Claims Rejected Under 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-3, 5-10, 15, 17-22, and 98-101 under 35 U.S.C. § 103(a) as being unpatentable over Hyndman et al. (Software to Determine Optimal Oligonucleotide Sequences Based on Hybridization Simulation Data. Biotechniques. 1996, Volume 20, Number 6, pages 1090-1096) taken in view of Southern (U.S. Patent Number 5,700,637), as indicated in the office action, mailed 01 July 2003, are maintained for reasons of record.

Applicants' arguments, filed 03 October 2003, indicates Hyndman et al. is deficient as discussed above and Southern does not cure these deficiencies. Applicants' arguments are found unpersuasive as discussed above (35 U.S.C. § 102 Rejection) and the claims remain obvious.

Claims 1-40 and 98-101 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rychlik et al. in view of Mitsuhashi et al. (U.S. Patent Number 5,556,749) or Hyndman et al. (Software to Determine Optimal Oligonucleotide Sequences Based on Hybridization Simulation Data. Biotechniques. 1996, Volume 20, Number 6, pages 1090-1096) further in view of Southern (U.S. Patent Number 5,700,637) further in view of The Chemical Rubber Co. (Handbook of Chemistry and Physics, 44th Edition, 1961, pages 9-10) and Kress et al. (Journal of Biomechanical Engineering, August 1987, Volume 109, Number 3, pages 218-225).

Rychlik et al. is applied as indicated above in the 35 U.S.C. § 102(b) Rejection. However, Rychlik et al. fails to teach the computation of probable errors (i.e. statistics), the target nucleotide sequence is RNA, conversion of parameters into dimensionless numbers, and electronically transferring the identified oligonucleotides to an oligonucleotide array.

Mitsuhashi et al. is applied as indicated above in the 35 U.S.C. § 102(b) Rejection. However, Mitsuhashi et al. fails to teach the computation of probable errors (statistics), conversion of parameters into dimensionless numbers, and electronically transferring the identified oligonucleotides to an oligonucleotide array.

Hyndman et al. is applied as indicated above in the 35 U.S.C. § 102 (b) Rejection. Hyndman et al. fails to teach to teach the conversion of parameters into dimensionless numbers and electronically transferring the identified oligonucleotides to an oligonucleotide array.

Southern (U.S. Patent Number 5,700,637) describes an apparatus and method for analyzing polynucleotide sequences and a method of generating oligonucleotide arrays, wherein a computer (i.e. electronically transfer data) is utilized to analyze and control the system (Abstract; Columns 6-9; Example 5, and claim 2).

'The Chemical Rubber Co. Handbook' is cited to establish that it is well known in the art to use standard deviation to compute probable errors (pages 9 and 10). Kress et al. is cited to establish that it is well known in the art to summarize results into dimensionless number(s) for easy comparison of several assays (Abstract; page 219 "Nomenclature"; and Figures 1 and 3-9). Rychlik et al. provides motivation for the combination by indicating the described nearest-neighborhood approach can be adapted for filter hybridization, since it is more accurate than methods based on numbers of AT and GC pairs (pages 8549-8550, lines 40-42 and 2-5, respectively). Mitsuhashi et al. provides motivation for the combination by indicating their disclosed invention is faster, more accurate, and allows the user to perform many types of analysis on the candidate probes (Column 6, lines 51-58). Hyndman et al. provides motivation for the combination by indicating the application of HYBsimulator to "design optimally specific DNA probes for dot blots, Southern blots, Northern blots, etc." (page 1093, column 2, beginning on line 25 to page 1094, column 1, line 19). Southern provides motivation for the combination by disclosing numerous potential applications for the novel method of analyzing nucleotide sequences (Columns 13-17, beginning on line 31). Thus, it would have been obvious to someone of ordinary skill in the art at the time of the invention to practice Rychlik et al. in view of Mitsuhashi et al. (U.S. Patent Number 5,556,749) or Hyndman et al. (Software to Determine Optimal Oligonucleotide Sequences Based on Hybridization Simulation Data. Biotechniques.

1996, Volume 20, Number 6, pages 1090-1096) further in view of Southern et al. further in view of The Chemical Rubber Co. (Handbook of Chemistry and Physics, 44th Edition, 1961, pages 9-10) and Kress et al. (Journal of Biomechanical Engineering, August 1987, Volume 109, Number 3, pages 218-225) to utilize the computer program(s) as an efficient method to design optimal oligonucleotide probe sequences based on thermodynamic hybridizability with statistical evaluations (i.e. probable errors), conversion of the parameters into dimensionless numbers, and transferring the resultant identified oligonucleotide probes to an oligonucleotide array manufacturing system, thereby providing a faster, more accurate, and broader application for the analysis of nucleotide sequences.

EXAMINER COMMENT

It is acknowledged by the Examiner the some of the above art rejections have not been previously applied, however, said rejections are newly applied taken in view of the U.S. Patent Number 6,512,588 (U.S. Application Number 09/021071).

EXAMINER INFORMATION

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 C.F.R. § 1.6(d)). The CM1 Fax Center number is either (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Channing S. Mahatan whose telephone number is (703) 308-2380. The examiner can normally be reached on M-F (8:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina M. Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

Date: November 3, 2003

Examiner Initials: CSM

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER
GROUP 1800
AU1631